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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/529,130	06/22/2000	MICHAEL JOHN DUGGAN	1581.0580000	2901

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 07/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/529,130	DUGGAN ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *63,65,66 and 68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63,65,66 and 68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *0704* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 63, 65, 66 and 68 are pending.

Applicants' amendment filed April 28, 2004 is acknowledged, and applicants' response has been fully considered. Claims 64, 67 and 69-70 have been cancelled, and claim 63 has been amended. Thus, claims 63, 65, 66 and 68 are examined. A proposed Examiner's Amendment was faxed to the applicant on June 30, 2004, however, the amendment has not been accepted at this time (see attached Interview Summary).

Rejection Withdrawn

Claim Rejections - 35 USC § 112

2. The previous rejection of claims 64, 67 and 69-70 under 35 U.S.C. 112, first paragraph, is withdrawn in view of applicants' cancellation of the claim, and applicants' response at pages 5-6 in the amendment filed April 28, 2004.

3. The previous rejection of claims 63-70 under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicants' cancellation of the claim, applicants' amendment of the claim, and applicants' response at page 7 in the amendment filed April 28, 2004.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 63, 65, 66 and 68 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an agent for treating pain, comprising

a galactose-binding lectin, a light (L) chain or a L-chain fragment of a clostridial neurotoxin comprising the active proteolytic enzyme domain, and a translocation domain of a clostridial neurotoxin heavy (H) chain, wherein the L-chain or L-chain fragment and the translocation domain of the clostridial neurotoxin are linked by disulfide bond to form LH_N, and the lectin and LH_N are linked by a bifunctional linker such as SPDP, does not reasonably provide enablement for an agent for treating pain, comprising a galactose-binding lectin, a L-chain or a L-chain fragment of a clostridial neurotoxin comprising the active proteolytic enzyme domain, and a translocation domain of a clostridial neurotoxin H-chain, wherein the lectin, L-chain or L-chain fragment, and the translocation domain are linked together by a covalent bond, and wherein the lectin is of bacterial origin, or the lectin has been treated with a modifying chemical and retains an ability to bind an oligosaccharide structure having an exposed galactose or N-acetylgalactosamine residue. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 63, 65, 66 and 68 encompass an agent for treating pain, comprising a galactose-binding lectin, an L-chain of a clostridial neurotoxin or its functional fragment, and a translocation domain of a clostridial neurotoxin H-chain, wherein the three components are linked together by a covalent bond, and wherein the lectin is of bacterial origin, or the lectin has been treated with a modifying chemical. The specification indicates an agent comprising a galactose-binding lectin or a fragment of galactose-binding lectin, an L chain of a clostridial toxin or its functional fragment, and a translocation domain of a clostridial toxin H-chain, can reduce and prevent the

transmission of pain signals from nociceptive afferents to projection neurons, wherein the agent can be prepared by conjugating a galactose-binding lectin with a derivative of clostridial neurotoxin via a linkage which may include a spacer, or can be expressed as a fusion protein from nucleic acid encoding an appropriate fragment of the galactose-binding lectin, in addition to a desired spacer, with a nucleic acid encoding all or part of a polypeptide of one serotype of neurotoxin (page 4, line 17-page 5, line 10; page 9, line 28-page 10, line 33). There are no indicia that the present application enables the full scope in view of an agent comprising a galactose-binding lectin, an L chain of a clostridial toxin or its functional fragment, and a translocation domain of a clostridial toxin H chain as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance as to how the full scope of the claim is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the absence or presence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claim is broad and encompasses unspecified variants regarding the linkage among the three components in the agent, e.g., the order of three components linked in the agent, and the modifying chemical used to contact the galactose-binding lectin, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

The examples indicate a conjugate of LH_N/A with a lectin from Erythrina cristagalli (ExL), E. corallodendron (EcL) or Glycine max (SBA) via a bifunctional linker SPDP, and the activity of ExL- LH_N/A in an electrophysiological or a behavior model of pain (Examples 1-8), however, there are no working examples indicating the direct linkage of a galactose-binding lectin to an L chain or H_N chain of a clostridal toxin in the agent, or the use of a modifying chemical to treat the lectin.

(3). The state of the prior art and relative skill of those in the art:

The related art (Foster *et al.*, WO 96/33273) indicates a targeting moiety such as lectin, antibody and hormone having specificity for the binding sites on the nociceptive afferent neurons can be used to prepare an agent for reducing the transmission of pain signals from nociceptive afferents to projection neurons (page 7, lines 15-17; page 13, lines 9-17), and an agent containing a derivatized NGF (nerve growth factor) linked to LH_N is prepared (Example 1). However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the making/use of an agent comprising a galactose-binding lectin, an L-chain or a functional L-chain fragment, and a translocation domain of a clostridial neurotoxin, wherein the three components are linked in different orders by a covalent bond, and the modified lectin treated with a modifying chemical to be considered enabling for variants.

(4). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to an agent for treating pain, comprising a galactose-binding lectin, an L-chain or a functional L-chain fragment of a clostridial neurotoxin,

and a translocation domain of a clostridial neurotoxin H-chain, wherein the three components are linked together by a covalent bond, and wherein the lectin is of bacterial origin, or the lectin has been treated with a modifying chemical. The specification indicates that the galactose-binding lectins can be purified from the seeds of genus *Erythrina* or *Glycine max*, or from bacteria *Pseudomonas aeruginosa* (page 7, line 12-page 9, line 15); and the agent for treating pain can be prepared from the lectin of *Erythrina* or *Glycine max,* which is conjugated to LH_N chain of botulinum toxin A via a bifunctional linker SPDP (Examples 1-8); or the agent can be expressed as a fusion protein from nucleic acid encoding an appropriate fragment of the galactose-binding lectin, in addition to a desired spacer, with a nucleic acid encoding all or part of a polypeptide of one serotype of neurotoxin (page 10, lines 1-9). However, the specification does not describe the making of an agent having the lectin directly linked to the L chain or the H_N chain of a clostridial toxin. Moreover, the specification does not disclose the treatment of a galactose-binding lectin with a modifying chemical, e.g., what modifying chemical is used, and what effect the modified lectin has in respect to the binding to a galactose or an N-acetylgalactosamine residue. Furthermore, there is no example indicating the preparation of a fusion protein of galactose-binding lectin, an L-chain or a functional L-chain fragment of a clostridial neurotoxin, and a translocation domain of a clostridial neurotoxin H-chain without a spacer; direct conjugation of a lectin to an L chain or an H_N chain of a clostridial toxin in the agent; or, the agent containing a lectin treated with a modifying chemical; and the use of the agent to treat pain. Since the specification fails to provide sufficient teachings on the agent having the three components linked in different orders by a covalent bond, and the treated lectins by a

modifying chemical, it is necessary to have additional guidance and to carry out further experimentation for assessing the effect of the agent having the three components linked in different orders by a covalent bond, or the agent containing the modified lectin.

(5). Predictability or unpredictability of the art:

The claim encompasses an agent for treating pain, comprising a galactose-binding lectin, an L-chain of a clostridial neurotoxin or a functional fragment thereof, and a translocation domain of a clostridial neurotoxin H-chain, wherein the three components are linked by a covalent bond, however, the making/use of the agent having the three components linked in different orders by a covalent bond, and the agent containing the treated lectins by a modifying chemical are not sufficiently described in the specification. Furthermore, there is no analogous art indicating the claimed agent. Thus, if the making/use of the agent is not taught by the specification or the prior art, the effect of the agent (e.g., L-lectin-H_N) in treating pain is not predictable.

(6). Nature of the Invention

The scope of the claim includes an agent having a galactose-binding lectin, an L-chain of a clostridial neurotoxin or a functional fragment thereof, and a translocation domain of a clostridial neurotoxin H-chain, where the three components are linked in different orders by a covalent bond, or the lectin is treated with a modifying chemical, but the specification does not provide sufficient teachings on these agents. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed variants, the effect of the agent is not predictable, and the

teaching in the specification is limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effect of the agent.

5. Claims 63, 65, 66 and 68 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 63, 65, 66 and 68 are directed to an agent for treating pain, comprising a galactose-binding lectin, an L-chain or it functional fragment of a clostridial neurotoxin, and a translocation domain of a clostridial neurotoxin H-chain, wherein the three components are linked by a covalent bond, and the lectin is a bacterial origin (claims 63(a), 65 and 66), or has been contacted with a modifying chemical and retains an ability to bind an oligosaccharide structure having an exposed galactose or N-acetylgalactosamine residue (claims 63(b) and 68). The specification indicates that galactose-binding lectin is a lectin binds to oligosaccharide structures having a terminal residue of galactose or N-acetylgalactosamine, and lectins are found in various life forms, the most commonly sources are the seeds of plants, e.g., the galactose-binding lectins from the seeds of genus *Erythrina* or *Glycine max*, or from bacteria *Pseudomonas aeruginosa* (page 7, line 12-page 9, line 15); and the agent can be prepared by conjugating a galactose-binding lectin with a derivative of clostridial neurotoxin via a linkage which may include a spacer (page 9, lines 28-31), or can be expressed as a fusion protein from nucleic acid encoding an appropriate fragment of the galactose-binding lectin, in addition to a desired spacer, with a nucleic acid encoding all or part of a

polypeptide of one serotype of neurotoxin (page 10, lines 1-9). However, the specification only describes the preparation of a conjugate of a plant lectin with an LH_N chain of botulinum toxin A via a SPDP linker, and the effect of the conjugate in treating pain (Examples 1-8), it does not describe the preparation of the conjugate of the lectin directly linked to an L chain or an HN domain of a clostridial toxin, and the fusion protein of galactose-binding lectin, an L-chain of a clostridial neurotoxin, and a translocation domain of a clostridial neurotoxin H-chain without a proper spacer, nor indicates the treatment of a galactose-binding lectin with a modifying chemical, e.g., what modifying chemical is used, and what effect the modified lectin has in respect to the binding to a galactose or an N-acetylgalactosamine residue. Furthermore, there is no example indicating direct linkage of a lectin to an L chain or an H_N chain of a clostridal toxin in the agent, or the modified lectin treated with a modifying chemical; and the use of the agent in treating pain. Without guidance on structure to function/activity of the lectin, one skilled in the art would not know which region or residue(s) of galactose-binding lectin is essential for function/activity and how to identify a functional galactose-binding lectin. The lack of description of structure to function/activity of the lectin and the agent comprising a lectin, an L chain and an H_N chain of a clostridial toxin with the three components linked in different orders by a covalent bond, and the lack of representative species for the agents and the modified galactose-binding lectins as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 63, 65, 66 and 68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 63 recites the limitation "N-acetylgalactosamine residue" in line 11. There is insufficient antecedent basis for this limitation in the claim. Claims 65, 66 and 68 are included in the rejection because they are dependent on rejected claims and do not correct the deficiency of the claim from which they depend.

Conclusion

7. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached at 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Patent Examiner

CMK
July 6, 2004